Remarks

Prior to this filing, claims 1, 6-11, 13-18, 21, 26-28, 32-34, and 38-45 were pending in this application. This filing is proper after final rejection at least because it does not enter any amendments, and it clarifies Applicants' position with regard to the pending rejections and thereby places the case in better posture for an appeal if such is necessary.

Examiner Interview

Applicants thank Examiner Huff for the courtesy of a telephone interview on July 9, 2008, with their representative, Dr. Anne Carlson. During the interview, the Final Office action dated May 12, 2008 was discussed. Specifically, the claim rejections under 35 U.S.C. §112, first paragraph and §103 were discussed. Though express agreement was not reached, it is believed that this response is in accordance with that discussion.

Withdrawal of Claim Rejection

Applicants thank Examiner Huff for withdrawing the rejection under 35 U.S.C. §112, second paragraph, of claims 26-28.

Claim Rejections Under 35 U.S.C. §112, first paragraph (enablement)

The previous rejection of claims 39-45 under 35 U.S.C. §112, as allegedly failing to comply with the enablement requirement, has been maintained. Claims 39-45 are directed to a method of screening for an agent that inhibits tumor recurrence. The Office continues to allege that "Applicant's specification has not provided any examples of such a screening process nor has the monoclonal antibody used in the treatment aspect of the specification been used in the screening assay. One of skill in the art recognizes that extensive research must be done both *in vitro* and *in vivo* before a compound can be said to inhibit tumors. Applicant has not even provided any *in vitro* data. Even if applicant had provided *in vitro* data, one could not extrapolate this teaching to *in vivo* use because the *in vitro* experimental data would not be drawn to subjects with tumor cells" (quoted from the June 8, 2007 Office action, page 4). The current Office action re-states, in particular, that "it is clear that TGF-beta is involved in a multitude of different processes. Because of this, one skilled in the art would not

readily believe that an assay that shows decreased TGF-beta activity would necessarily result in an agent that inhibit[s] tumor recurrence" (Office action at page 3). Applicants traverse this rejection.

The specification describes agents as "any substance, including, but not limited to, an antibody, chemical compound, small molecule, peptide mimetic, peptide or protein" (specification at page 7, lines 4-5). Thus, as discussed with Examiner Huff during the telephone interview, the 1D11 monoclonal antibody of the claimed methods is an "agent," which was previously shown to inhibit TGF-beta growth promoting activity (see Example 5 in Dasch *et al.*, U.S. Patent No. 6,090,383). Moreover, the specification clearly presents data in Example 5 (page 33, line 30 though page 34, line 28) illustrating the effect of the 1D11 antibody on tumor recurrence. For example, Example 5 teaches administration of a collection of antibodies (anti-CD4 antibody, anti-TGF-beta 1D11 antibody, or the isotype matched monoclonal antibody) to tumor-bearing mice producing increased levels of TGF-beta and that the mice administered the 1D11 antibody were protected from the recurrence of tumor, compared to mice contacted with a different antibody (agent). In addition, the specification at Example 3 (page 31, line 32 through page 32, line 22) teaches an assay that measures the recovery of cytolytic activity of CTLs (which activity is suppressed when cultured with TGF-beta), when the cells are also cultured in the presence of the 1D11 antibody. Thus, Examples 3 and 5 teach:

(i) contacting a TGF-beta receptor-expressing immune cell (*i.e.*, CTL) with TGF-beta ;

(ii) contacting the TGF-beta receptor-expressing immune cell with an agent (*i.e.*, 1D11); and

(iii) assaying for a decrease in activity of TGF-beta signaling in the TGF-beta receptor-expressing immune cell, as compared to a TGF-beta receptor-expressing control immune cell of the same type not contacted with the agent (*i.e.*, measuring change in CTL cytolytic activity in presence of 1D11),

(iv) wherein the decrease in activity of TGF-beta signaling in the TGF-beta receptor-expressing immune cell (*i.e.*, increased cytolytic activity) is indicative of an agent that inhibits tumor recurrence in a subject, thereby screening for an agent that inhibits tumor recurrence.

Accordingly, the specification provides at least one working example of an agent (1D11 antibody) which has been demonstrated, in a screening assay, to inhibit tumor recurrence *in vivo* in an animal model, and which is of the type Applicants teach can be identified using the claimed methods.

MPEP §2164.02 clearly states that "[t]he presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure . . . one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims." In the current instance, Applicants' teaching of at least one agent (the 1D11 antibody) that has the desired function and that can be identified in Applicants' claimed methods is sufficient for one of ordinary skill to be able to extrapolate across the entire scope of claims 39-45.

The specification provides all the information necessary for one of skill in the art to perform the claimed method of screening for any agent without undue experimentation. For example, in addition to the working example, the specification provides:

(i) various *in vitro* and *in vivo* techniques for identifying which agents can inhibit tumor recurrence (page 26, line 5 through page 27, line 18);
(ii) representative candidate agents that can be used to block the TGF-beta signaling pathway and inhibit tumor recurrence (page 22, line 31 through page 24, line 20);
(iii) example *in vitro* assays to measure the effect of such agents on the TGF-beta signaling pathway (page 24, line 23 through page 25, line 5); and
(iv) example *in vivo* assays to measure the effect of such agents on the TGF-beta signaling pathway (page 25, lines 7-38).

Further, at the time the application was filed it was well known to those of skill in the art how to use *in vitro* assays to test the effectiveness of various agents for clinical use. It was also well known at the time how to test promising candidate agents *in vivo* using any one of a number of animal models. Applicants submit that, given the state of the art at the time of filing and the guidance in the specification, it would merely be **routine** to perform the method of screening for an agent that inhibits tumor recurrence. Thus, Applicants contend that the specification provides sufficient guidance for one of skill in the art to understand and perform the claimed screening methods and is therefore enabled across the entire scope of these claims.

In light of the above arguments, Applicants submit that claims 39-45 are fully enabled by the specification. Applicants request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Claim Rejections Under 35 U.S.C. §103

Dasch *et al.* in view of Barbera-Guillem and Rosenblum

Claims 1, 6-9, 11, 13-15, 21, 26-28, and 32-34 are rejected under 35 U.S.C. §103 as obvious over Dasch *et al.* (U.S. Patent No. 6,090,383) in view of Barbera-Guillem (U.S. Patent No. 6,224,866) and Rosenblum (U.S. Patent Application No. 2005/0214307) because the combination of references allegedly teaches "that compounds that treat tumors can also be used to treat tumor recurrence" (Office action dated November 8, 2007, at page 5). Applicants thank Examiner Huff for removing Zavada *et al.* (U.S. Patent No. 6,297,041) as a reference in this rejection in view of Applicants' previous arguments. However, Applicants strenuously traverse the revised rejection.

The United States Patent and Trademark Office has provided Examination Guidelines for Determining Obviousness Under 35 U.S.C. §103 in View of the Supreme Court Decision in *KSR International Co.* v. *Teleflex Inc.* Based on those Guidelines, the Office must provide the appropriate rationale to support rejections under 35 U.S.C. §103.

As admitted in the November 2007 Office action, Dasch *et al.* does not specifically discuss the treatment of tumor recurrence (nor does Dasch *et al.* disclose methods of *inhibiting* tumor recurrence). The current Office action combines Dasch *et al.* with two other references (Barbera-Guillem and Rosenblum) which allegedly make up for the deficiency of Dasch *et al.* Applicants respectfully disagree.

As discussed with Examiner Huff, Applicants submit that the claimed elements could not have been combined, even in view of Dasch *et al.*, Barbera-Guillem, and Rosenblum, to **predictably** yield the claimed invention. Barbera-Guillem and Rosenblum both disclose antibodies, but that is where the similarity with the claimed methods ends. For example, Barbera-Guillem discloses the use of an

immunotherapeutic composition that binds B cells (for example, anti-CD20, anti-Lym-1, or anti-CD19 antibodies) in order to cause B cell depletion and reduce a pro-tumor immune response (see for example, column 3, line 3 through column 4, line 14; column 5, lines 57-63). Barbera-Guillem does not teach the 1D11 antibody. In contrast to the antibodies disclosed in Barbera-Guillem, the 1D11 antibody of the claimed methods binds TGF-beta which is released from non-T-non-B cells, and the antibody blocks an immunosuppressive effect of TGF-beta (see, for example, the specification at page 31, lines 26-29 and Example 5). Thus, the antibodies disclosed in Barbera-Guillem function by a completely different mechanism than the 1D11 antibody, and would have no effect on TGF-beta or cells producing TGF-beta. The Barbera-Guillem antibodies therefore provide no reliable guidance for the activities exhibited by the 1D11 antibody, nor are they at all predictive of Applicants' use of this antibody.

Rosenblum discloses that one specific agent used in the treatment of tumors can be used to prevent tumor recurrence (paragraph [0043]). The "agent" of Rosenblum is an immunoconjugate comprised of a monoclonal antibody or a single chain antibody linked to a cytotoxic moiety, where the antibody moiety targets the cytotoxic moiety to the tumor cell. The purpose of the antibody moiety aspect of that "agent" is to target the cytotoxin (the active component of the immunoconjugate) to the tumor cell. Thus, the "antibody" disclosed in Rosenblum is not, *per se*, inhibiting the tumor recurrence. Like Barbera-Guillem, Rosenblum does not disclose the 1D11 antibody or another antibody that inhibits TGF-beta activity. Nothing about the Rosenblum agent would provide reliable guidance to one of ordinary skill in the art for the activities exhibited by the 1D11 antibody, nor is it predictive in any way of Applicants' use of this antibody.

Antibodies, like drugs, are a generic class of compounds. Just as one would not conclude that two completely different drugs, having different mechanisms of action, could be used to treat the same disease, one should not extrapolate that two different antibodies that function by wholly different mechanisms would have **predictably** the same biological effect. The mere fact that Rosenblum and Barbera-Guillem disclose antibodies or antibody fusion proteins that are used in some way to inhibit tumor recurrence is not, on its own, **predictive** of the claimed method, which uses a completely different antibody having a completely different mechanism of action than the antibodies disclosed in

these references (see Amendment and Response submitted on April 8, 2008, for details related to the mechanism of action of the 1D11 antibody). Neither Barbera-Guillem nor Rosenblum disclose an antibody that binds TGF-beta or that blocks an immunosuppressive effect of TGF-beta, as required by the claims, which are specifically directed to the use of the 1D11 antibody. As antibodies belong to the "unpredictable" art of biotechnology, and because the antibodies disclosed in Barbera-Guillem and Rosenblum function by different mechanisms than the 1D11 antibody, one of skill in the art **would not have predicted** that the combination of elements in these references and in Dasch *et al.* would yield the claimed invention.

Applicants respectfully submit that the disclosures of Barbera-Guillem and Rosenblum are not predictive that an antibody which blocks an immunosuppressive effect of TGF-beta would inhibit recurrence of a tumor and these references cannot be combined with Dasch *et al.* Accordingly, Applicants requests that this rejection be withdrawn.

Dasch *et al.* in view of Barbera-Guillem, Rosenblum, and Suthanthiran *et al.*

Claims 1, 6-11, 13-15, 21, 26-28, 32-34 and 38 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Dasch *et al.* in view of Barbera-Guillem, Rosenblum, and Suthanthiran *et al.* (U.S. Publication No. US 2004-0197333). Applicants thank Examiner Huff for removing Zavada *et al.* (U.S. Patent No. 6,297,041) as a reference in this rejection in view of Applicants' previous arguments. However, Applicants respectfully traverse the revised rejection.

The Office action states that Suthanthiran *et al.* discloses the use of TGF-beta antagonists, including monoclonal antibodies, "to *treat* a variety of different cancers known to be associated with TGF-beta" (Office action at page 7, emphasis added). However, Suthanthiran *et al.* does not teach the use of TGF-beta antagonists to *inhibit the recurrence* of a tumor that has escaped tumor immunosurveillance. Nor does Suthanthiran *et al.* disclose the concept of tumor recurrence. Thus, Suthanthiran *et al.* does not make up for the deficiencies of Dasch *et al.*

As discussed above, the disclosures of Barbera-Guillem and Rosenblum are not predictive that an antibody that blocks an immunosuppressive effect of TGF-beta would inhibit recurrence of a tumor,

and Dasch *et al.* and Suthanthiran *et al.* do not implicitly or explicitly teach all elements of the claimed methods. Thus, Applicants' claims are non-obvious over the combination of cited references. Withdrawal of this rejection is requested.

Dasch *et al.* in view of Barbera-Guillem, Rosenblum, and Terabe *et al.*

Claims 1, 6-9, 11, 13-18, 21, 26-28, 32-34 and 38 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Dasch *et al.* in view of Barbera-Guillem, Rosenblum, and Terabe *et al.* (*Nature Immunology*, 1:515-520, 2000). Applicants thank Examiner Huff for removing Zavada *et al.* (U.S. Patent No. 6,297,041) as a reference in this rejection in view of Applicants' previous arguments. However, Applicants respectfully traverse the revised rejection.

The Office action states that Terabe *et al.* shows that the "assays of claims 16-18 are known in the art . . . and are used in tumor immunosurveillance" (Office action at page 8). However, Terabe *et al.* does not teach the use of TGF-beta antagonists to *inhibit the recurrence* of a tumor that has escaped tumor immunosurveillance. As discussed above, Dasch *et al.* does not teach methods of inhibiting tumor recurrence. Thus, Terabe *et al.* does not make up for the deficiencies of Dasch *et al.* In addition, as discussed above, the disclosures of Barbera-Guillem and Rosenblum are not predictive that an antibody that blocks an immunosuppressive effect of TGF-beta would inhibit recurrence of a tumor and these references cannot be combined with Dasch *et al.* Thus, Applicants' claims are non-obvious over the cited references. Withdrawal of this rejection is requested.

Request for Examiner Interview

Applicants believe the application is in condition for allowance and such action is requested. If if the present rejections are maintained, or an additional rejection is asserted, Examiner Huff is formally requested to contact the undersigned in order to arrange a telephonic interview prior to issuance of the next Office action. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview can be arranged in advance by a written request.

Respectfully submitted,

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